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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/433,418	11/04/99	EPSTEIN J	244/023

022249
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HM12/0925

EXAMINER	
BAHAR, M	
ART UNIT	**PAPER NUMBER**
1617	10

DATE MAILED: 09/25/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Offic Action Summary	Application No. 09/433,418	Applicant(s) EPSTEIN, JOEL B.	
	Examiner Mojdeh Bahar	Art Unit 1617	

-- The MAILING DATE of this communication appears on the c ver sheet with the correspondence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 July 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-19 and 21-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-19 and 21-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's response to the first office action of March 28, 2001, submitted July 2, 2001 (Paper No. 9) is acknowledged.

Applicant's remarks and amendments submitted July 2, 2001 in Paper No. 9 are persuasive to remove the rejection under 35 U.S.C. 112 and objections in the previous office action. Note that the grounds for rejecting claim 1 under 35 U.S.C. 112, second paragraph is removed since the expression "purine analog" is omitted from the claim.

Claims 1, 2-19 and 21-36 are herein examined on the merits.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lozada in view of Qi et al. (WO 97/31921).

Lozada teaches a method of treating patients with chronic inflammatory mucocutaneous disease having oral ulcerations including lichen planus, pemphigus vulgaris and bullous pemphigoid comprising administering azathioprine (an immunosuppressive agent), and a steroidal antiinflammatory agent see page 257 first full paragraph, see also MATERIALS AND METHODS. Lozada teaches that Azathioprine is administered from 5 mg every other day to 100 mg/day, see pages 258 Drugs and Results. See also page 259, Col. 2, first full paragraph as well as page 258 Adverse effects.

Lozada does not teach that the composition can be in form of a liquid, solution, suspension, emulsion as well as lotions, ointments and creams. Neither does it teach a method of using the said composition in treating systemic lupus, graft-versus-host disease, lichenoid changes and aphthae associated with HIV and aphthous stomatitis. Lozada et al. does not teach the particular concentration of azathiporine in a solution, nor does it teach the use of the azathioprine solution to rinse the mouth.

Qi et al. (WO 97/31921) teaches a method of administering an immunosuppressive composition in the treatment of autoimmune disorders comprising administering a compound such as azathioprine, page 19, lines 8-17. The composition can be in form of a liquid, solution, suspension, emulsion as well as lotions, ointments and creams, page 14, line 20-25, see also page 15, lines 1-15. Qi et al. (WO 97/31921) also teaches a method of using the said composition in treating systemic lupus as well as graft-versus-host disease, page 5, line 21-24, page 17, line 15-17. Qi et al. (WO 97/31921) further teaches a method of effecting immunosuppression in a subject generally and a method of inhibiting (i.e. preventing) graft-versus-host disease in particular, page 5, lines 21-24.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use a liquid, solution, suspension, emulsion as a form of delivery for the composition in the method taught by Lozada. It would have also been obvious to employ the treat any auto-immune disease resulting in ulcerations in the mouth such as oral graft versus host disease, systemic lupus, aphthous stomatitis and lichenoids and aphthae associated with AIDS with a composition comprising azathioprine. It would have also been obvious to use the

composition in a mouth wash and rinse the effective area with the said composition. Furthermore, optimization of the concentrations of the mouthwash are obvious.

One of ordinary skill in the art would have been motivated to employ azathioprine to treat other similar ulcerative auto-immune disorders of the mouth because azathioprine is known to be useful in the treatment and prevention of auto-immune diseases of the mouth having oral ulcerations such as lichen planus, pemphigus vulgaris and bullous pemphigoid. Moreover, one of ordinary skill would have been motivated to use a delivery form that comes in contact with the affected area of the mouth because for example, oral liquid, solution, syrup, suspension and emulsion dosage forms known, and topical and oral administration are known for azathioprine composition administration in auto-immune disease treatment. Therefore azathioprine would be reasonably expected to be useful in methods of treating ulcerative auto-immune diseases of the mouth. The optimization of amounts of actives and their concentrations is within the purview of skilled artisan. Furthermore, rinsing the mouth with a therapeutic composition known to treat auto-immune disorders of the mouth is obvious to the skilled artisan because the ulcerations resulting from the auto-immune disease of the mouth are localized and the optimization of dosage regimens is also obvious as being within the skill of the artisan.

Applicant argues that a *prima facie* case of obviousness has not been established because there is no motivation to combine the teachings of Lozada and Qi, the two cited references in the previous office action. Applicant's arguments in this regard have been considered but are not found persuasive. Motivation to combine the two references has been set forth in the previous office action, see particularly pages 5 and 6. Lozada teaches the employment of azathioprine (an immunosuppressive agent) along with a steroidal anti-inflammatory agent (prednisone) in a

method of treating patients with chronic inflammatory mucocutaneous disease having oral ulcerations including lichen planus, pemphigus vulgaris and bullous pemphigoid. Qi et al teaches a method of administering immunosuppressive agents including azathioprine in form of a liquid, solution, suspension, emulsion as well as lotions, ointments and creams, page 14, line 20-25, see also page 15, lines 1-15. Qi et al. (WO 97/31921) also teaches a method of using the said composition in treating systemic lupus as well as graft-versus-host disease. One of ordinary skill in the art would have been motivated to employ the immunosuppressive azathioprine, alone or in combination with an anti-inflammatory agent to treat autoimmune diseases because azathioprine is known to be an immunosuppressive agent known to be employed in treating lichen planus, pemphigus vulgaris and bullous pemphigoid and graft-versus-host disease.

Applicants further argue that Lozada teaches that the anti-inflammatory agent and azathioprine act synergistically. One of ordinary skill in the art cannot conclude that the immunosuppressive activities of azathioprine will be diminished if the anti-inflammatory agent is removed. Lozada teaches that the combination of azathioprine with prednisone yields synergistic effects. This is not to say that azathioprine cannot be expected to exhibit similar therapeutic effects when used alone. Furthermore, note that the instant claims 11 and 29 require the incorporation of an anti-inflammatory agent along with azathioprine.

Finally, applicants argue that Qi teaches a composition comprising azathioprine and a triptolide analog and thus does not teach the instant invention. Following the same line of reasoning provided immediately above, Qi teaches that compositions comprising azathioprine (an immunosuppressant) are employed in methods of treating autoimmune diseases such as graft-versus-host disease.

The two references teach that azathioprine has been employed in treating auto-immune diseases of the mouth. Applicants refer to some prior art references on page 9 of the response, however there is no showing of diminished side effects of azathioprine in the instant invention. Nor is there any data indicating that a composition **consisting essentially of** azathioprine yields unexpected results when compared to compositions **comprising** azathioprine.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mojdeh Bahar whose telephone number is (703) 305-1007. The examiner can normally be reached on (703) 305-1007 from 8:30 a.m. to 6:30 p.m. Monday, Tuesday, Thursday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Minna Moezie, J.D., can be reached on (703) 308-4612. The fax number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Mojdeh Bahar
Patent Examiner
September 19, 2001

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